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Subject: Recommendation for Dr. Jun Yin
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Gentlepersons:

I am writing in very strong support of Dr. Jun Yin's application for a faculty position at Indiana University. I have known Dr. Yin for the past two years in the context of a collaborative research project involving my laboratory and the laboratories of Prof. Christopher T. Walsh at Harvard Medical School and Professor Marianne Wessling-Resnick at the Harvard School of Public Health.

Dr. Yin received the Ph.D. degree in Chemistry from the University of California at Berkeley in 2003. He studied antibody engineering and the immunological evolution of catalytic antibodies. In three first-author papers in *Biochemistry,* the *Proceedings of the National Academy of Sciences of the United States of America* and the *Journal of Molecular Biology*, Dr. Yin reported his discoveries concerning antibody-antigen interactions based on a series of eight crystal structures he solved using X-ray crystallography. The crystal structures solved by Dr. Yin showed the binding of a number of

antigens to their cognate antibodies, either in the wild-type state or in the affinity-matured state that corresponded to different stages of immunological antibody evolution. Close examination of these crystal structures allowed Dr. Yin to elucidate the different antigen-binding modes of the wild-type and affinity-matured antibodies and to discover the mechanism utilized by the immune system to introduce mutations into the wild-type antibody. These evolutionary mutations optimize antigen binding in the process of transforming the wild-type antibody to the affinity-matured antibody, which was found to have higher binding affinity and specificity for the disease antigens. Dr. Yin's ground-breaking research in this area has significantly advanced our knowledge about how the immune system generates highly specific antibodies that target and eliminate pathogenic organisms and cancer cells, and his research has important implications for guiding antibody therapies and vaccine generation for the treatment of cancer and infectious diseases.

Dr. Yin has also contributed significantly to the field of antibody engineering. In order to treat patients who have defective immune system - such as AIDS patients and cancer patients - antibodies must be specifically engineered to bind and eliminate disease antigens. Using an innovative phage display strategy, Dr. Yin reported in the *Journal of the American Chemical Society* that he could modify the antibody structure and enhance the activity of a heme-binding peroxidase antibody by a factor of 10. This represented a milestone in antibody engineering, because Dr. Yin demonstrated that antibodies could be tailor-made to acquire a desired function and activity. Using Dr. Yin's approach, many therapeutic antibodies with high binding affinity and specificity for disease antigens can now be developed in vitro. These functionally optimized antibodies can then be administrated to patients for therapeutic benefit.

Dr. Yin is currently a postdoctoral research fellow at Harvard Medical School working on engineering biosynthetic enzymes for the

generation of new antibiotics. Dr. Yin's recent research, published as two papers in the *Journal of the American Chemical Society*, showed that enzymes involved in the antibiotic biosynthetic machinery can be used for protein labeling and high-throughput screening of drug leads from small molecule libraries. These findings have the potential to significantly enhance the efficiency and shorten the length of time required for drug discovery. The *Chemical and Engineering News* has featured Dr. Yin's research achievements on engineering antibiotic biosynthetic enzymes, and my own laboratory at Harvard Medical School is now using the protein labeling method developed by Dr. Yin to study the molecular mechanisms of signaling and trafficking by transmembrane receptors important in the pathophysiology of human disease.

In our collaborative research project, which has recently been published in *Chemistry and Biology* and the *Proceedings of the National Academy of Sciences of the United States of America* and featured as a "research highlight" in *Nature Methods*, Dr. Yin and colleagues have used his protein labeling method to specifically label ligands and receptors at the cell surface of human cells in culture. This method is based on the specificity of a bacterial enzyme for covalent attachment of fluorescently labeled coenzyme A conjungates to a bacterial sequence that has been inserted into the receptor of interest. Together with single-cell fluorescence resonance energy transfer (FRET) imaging techniques, this novel labeling method has allowed us to show for the first time that transferrin receptor 1 and its ligand transferrin remain associated throughout the endocytic/exocytic cycle in living cells, from cell surface binding of iron-conjugated transferrin to endocytosis of iron-transferrin to exocytosis of apotransferrin to cell surface release of apotransferrin. Furthermore, Dr. Yin's labeling method will enable many further studies of receptor and ligand signaling and trafficking in a wide variety of important biological systems.

In all of my interactions with Dr. Yin, I have found him to be a most engaging, enthusiastic, energetic, hard-working, talented and insightful collaborator. He reads widely in the literature and asks thoughtful and penetrating questions. He designs insightful experiments with appropriate controls, and analyzes his results with expertise and care. Dr. Yin collaborates well with others in the laboratory and he has excellent written and oral communications skills.

I have complete confidence that Dr. Yin will become an outstanding independent investigator at a leading academic institution. Indeed, you would be very fortunate to recruit him as a junior faculty member and colleague at your institution. Please feel free to contact me if I can provide additional information relevant to your deliberations. Sincerely yours,

David E. Golan, M.D., Ph.D.

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